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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/525,783 | 02/28/2005 | Richard Keith | 100822-1P US | 8524 |

22466 7590 02/07/2008

ASTRA ZENECA PHARMACEUTICALS LP
GLOBAL INTELLECTUAL PROPERTY
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WILMINGTON, DE 19850-5437

| EXAMINER | |
|---|---|
| OLSON, ERIC | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1623 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/07/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/525,783 | KEITH, RICHARD | |
| | Examiner | Art Unit | |
| | Eric S. Olson | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15 and 24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Detailed Action

This office action is a response to applicant's communication submitted October 23, 2007 wherein Applicant traverses the grounds of rejection made in the previous office action. This application is a national stage application of PCT/SE03/01352, filed September 1, 2003, which claims priority to foreign application SE0202598-9, filed September 2, 2002.

Claims 15 and 24-28 are pending in this application.

Claims 15 and 24-28 as amended are examined on the merits herein.

The following rejections of record in the previous office action are maintained:

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 24, 26, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al. (US patent 5902814, of record in previous office action) in view of Scolnick (PCT international publication WO95/06470, of record in previous action) further in view of Stalker et al. (of record in previous office action) Gordon et al. discloses a number of spiro-azabicyclo[2.2.2]octane compounds, including spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one hydrochloride. (column 1, lines 30-49, column 6, line 33 – column 7, line 33) These compounds are useful in the manufacture

of a medicament for the treatment of a number of conditions including Alzheimer's disease. (column 4, lines 27-41, column 5, lines 10-16) Gordon et al. does not disclose a combination of this compound with rosuvastatin, a pharmaceutical composition comprising such a combination, or a method of treating Alzheimer's disease using such a composition.

Scolnick et al. discloses a method for treating and arresting the development of Alzheimer's disease by administering an HMG-CoA reductase inhibitor such as Lovastatin, simvastatin, pravastatin , or fluvastatin. (P. 3, lines 25-32)

Stalker et al. discloses that Rosuvastatin has the same or similar function as simvastatin, lovastatin, and fluvastatin, being an HMG-CoA reductase inhibitor.

It would have been obvious to one of ordinary skill in the art to modify the invention of Gordon et al. by combining spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one hydrochloride with rosuvastatin to produce the combinations described by instant claims 15 and 24, and the pharmaceutical composition of claim 26, and by administering the composition to a patient suffering from Alzheimer's disease as described by instant claims 27 and 28. One of ordinary skill in the art would have been motivated to produce this combination because spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one hydrochloride and statins were known to be useful for the treatment of Alzheimer's disease and because Stalker et al. discloses that rosuvastatin functions by the same mechanism as other statins mentioned by Scolnick as being useful for treating Alzheimer's disease. One of ordinary skill in the art would reasonably have expected success because combining known therapeutic compounds, adding a

pharmaceutically acceptable carrier, and administering the composition to a patient is well within the ordinary and routine level of skill in the art.

It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted October 23, 2007, with respect to the above ground of rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the cited references do not disclose that statins reduce levels of amyloid beta, thereby improving Alzheimer's disease. However, the mechanism by which the claimed invention operates does not serve to render said invention non-obvious over the prior art if the prior art already motivates one of ordinary skill in the art to make the invention for some other reason. The simple expectation of additive effects for the combination of two known therapeutic agents is sufficient to motivate one of ordinary skill in the art to combine two known inventions. Furthermore, Applicant's disclosure provides no evidence of unexpected, superadditive, or synergistic results for the claimed compositions and methods, As no actual experimental data re presented in the specification. Therefore the rejection is deemed proper and maintained.

Claims 15, 25, 26, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peters et al. (PCT international publication WO9854189, of record in previous office action) in view of Scolnick (PCT international publication WO95/06470, of record in previous action) further in view of Stalker et al. (of record in previous office action)

Peters et al. discloses a range of nicotininc receptor agonists useful for treating a number of diseases including Alzheimer's disease and Parkinson's disease. (p. 4, lines 25-36) The compounds have a general formula which includes (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] within its general teaching. (p. 5, line 24 – p. 6, line 15, p. 9, lines 14-21, when A = O, B = $CH_2$, C = N, D = F = CH, E = C-3-furanyl) Peters et al. does not teach a composition of (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and rosuvastatin or a method of treating Alzheimer's or Parkinson's disease by administering such a composition.

Scolnick et al. discloses a method for treating and arresting the development of Alzheimer's disease by administering an HMG-CoA reductase inhibitor such as Lovastatin, simvastatin, pravastatin , or fluvastatin. (P. 3, lines 25-32)

Stalker et al. discloses that Rosuvastatin has the same or similar function as simvastatin, lovastatin, and fluvastatin, being an HMG-CoA reductase inhibitor.

It would have been obvious to one of ordinary skill in the art to modify the invention of Peters et al. by combining (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] with rosuvastatin to produce the combinations described by instant claims 15 and 25, and the pharmaceutical

composition of claim 26, and by administering the composition to a patient suffering from Alzheimer's disease as described by instant claims 27 and 28. One of ordinary skill in the art would have been motivated to produce this combination because (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and statins were known to be useful for the treatment of Alzheimer's disease in the prior art and because Stalker et al. discloses that rosuvastatin functions by the same mechanism as other statins mentioned by Scolnick as being useful for treating Alzheimer's disease. One of ordinary skill in the art would have been motivated to specifically use (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] in the composition because this compound is within the general range of compounds disclosed by Peters et al. to be useful for treating Alzheimer's disease. One of ordinary skill in the art would reasonably have expected success because combining known therapeutic compounds, adding a pharmaceutically acceptable carrier, and administering the composition to a patient is well within the ordinary and routine level of skill in the art.

It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted October 23, 2007, with respect to the above ground of rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the cited references do

not disclose that statins reduce levels of amyloid beta, thereby improving Alzheimer's disease. However, the mechanism by which the claimed invention operates does not serve to render said invention non-obvious over the prior art if the prior art already motivates one of ordinary skill in the art to make the invention for some other reason. The simple expectation of additive effects for the combination of two known therapeutic agents is sufficient to motivate one of ordinary skill in the art to combine two known inventions. Furthermore, Applicant's disclosure provides no evidence of unexpected, superadditive, or synergistic results for the claimed compositions and methods, As no actual experimental data re presented in the specification. Therefore the rejection is deemed proper and maintained.

The following new grounds of rejection are introduced:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 24, and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al. (US patent 5902814, of record in previous office action) in view of Lilienfeld et al. (US patent publication 2005/0222122, cited in PTO-892) Gordon et al. discloses a number of spiro-azabicyclo[2.2.2]octane compounds, including spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one hydrochloride. (column 1, lines

30-49, column 6, line 33 – column 7, line 33) These compounds are useful in the manufacture of a medicament for the treatment of a number of conditions including Alzheimer's and Parkinson's disease. (column 4, lines 27-41, column 5, lines 10-16) Gordon et al. does not disclose a combination of this compound with rosuvastatin, a pharmaceutical composition comprising such a combination, or a method of treating Alzheimer's or Parkinson's disease using such a composition.

Lilienfeld et al. discloses that cholesterol increases amyloid beta formation in the brain, and that statins decrease said amyloid production. (p. 1, paragraphs 0011-0014) Lilienfeld et al. also discloses a method of treating dementia comprising administering a combination of galantamine and a statin. (p. 2, paragraph 0015) The statin is selected from a group including rosuvastatin. (p. 2, paragraph 0016) Dementias treatable in this manner include dementias resulting form Alzheimer's and Parkinson's diseases. (p. 2, paragraph 0022)

It would have been obvious to one of ordinary skill in the art to modify the invention of Gordon et al. by combining spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one hydrochloride with rosuvastatin to produce the combinations described by instant claims 15 and 24, and the pharmaceutical composition of claim 26, and by administering the composition to a patient suffering from Alzheimer's or Parkinson's disease as described by instant claims 27 and 28. One of ordinary skill in the art would have been motivated to produce this combination because spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one hydrochloride and rosuvastatin are both shown to be useful for the treatment of Alzheimer's and Parkinson's disease. One of

ordinary skill in the art would reasonably have expected success because combining known therapeutic compounds, adding a pharmaceutically acceptable carrier, and administering the composition to a patient is well within the ordinary and routine level of skill in the art.

It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Claims 15, 25, and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peters et al. (PCT international publication WO9854189, of record in previous office action) in view of Lilienfeld et al. (US patent publication 2005/0222122, cited in PTO-892) Peters et al. discloses a range of nicotininc receptor agonists useful for treating a number of diseases including Alzheimer's disease and Parkinson's disease. (p. 4, lines 25-36) The compounds have a general formula which includes (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] within its general teaching. (p. 5, line 24 – p. 6, line 15, p. 9, lines 14-21, when A = O, B = $CH_2$, C = N, D = F = CH, E = C-3-furanyl) Peters et al. does not teach a composition of (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and rosuvastatin or a method of treating Alzheimer's or Parkinson's disease by administering such a composition.

Lilienfeld et al. discloses that cholesterol increases amyloid beta formation in the brain, and that statins decrease said amyloid production. (p. 1, paragraphs 0011-0014) Lilienfeld et al. also discloses a method of treating dementia comprising administering a combination of galantamine and a statin. (p. 2, paragraph 0015) The statin is selected from a group including rosuvastatin. (p. 2, paragraph 0016) Dementias treatable in this manner include dementias resulting form Alzheimer's and Parkinson's diseases. (p. 2, paragraph 0022)

It would have been obvious to one of ordinary skill in the art to modify the invention of Gordon et al. by combining (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] with rosuvastatin to produce the combinations described by instant claims 15 and 24, and the pharmaceutical composition of claim 26, and by administering the composition to a patient suffering from Alzheimer's or Parkinson's disease as described by instant claims 27 and 28. One of ordinary skill in the art would have been motivated to produce this combination because (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] and rosuvastatin are both shown to be useful for the treatment of Alzheimer's and Parkinson's disease. One of ordinary skill in the art would have been motivated to specifically use (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] in the composition because this compound is within the general range of compounds disclosed by Peters et al. to be useful for treating Alzheimer's disease, and because all the structural elements of this compound are recited as possible embodiments of the variable positions in the generic structure. One of ordinary skill in

the art would reasonably have expected success because combining known therapeutic compounds, adding a pharmaceutically acceptable carrier, and administering the composition to a patient is well within the ordinary and routine level of skill in the art.

It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

## ***Conclusion***

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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1/30/08

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